Betwixt Gene and Behavior (Commentary on the Paper by J. D. Sinclair)

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Article:

Behavior genetics seeks to make meaningful statements about individual behavior from knowledge of genes. It is interdisciplinary in the extreme because it attempts to span several levels of reality in one inferential leap. By level of reality, I mean the level at which matter is organized, as in this scheme giving an example at each level:

Society (deme)
↕
Individual (mouse)
↕
Organ (brain)
↕
Tissue (hippocampus)
↕
Cell (pyramidal neuron)
↕
Organelle (mitochondrion)
↕
Macromolecule (DNA)
↕
Molecule (amino acid)
↕
Atom (carbon)

A gene is a macromolecule which codes for the structure of a protein. Lehninger (1967) points out, "The ascent from simple self-assembling systems such as oligomeric proteins and enzyme complexes to the level of supramolecular organization of subcellular organelles is a very steep one. In making it we cross a boundary to a level of organization at which the self-assembly principle doubtless operates in microscopic regions, but cannot account for the biogenesis of the organelle," (p. 91). The ascent from gene to behavior is precarious indeed.

Once the simplistic notion of rigid genetic specification of behavior is rejected, which the traditional $P = G + E$ and more realistic $X = H \cdot E$ formulae most emphatically do, the challenge is to understand how and why genetic variation is associated with behavioral differences. Some practitioners seem to think this goal can be achieved by measuring behavior and nucleotide sequences of the individual, then connecting the two with multivariate analysis. On the other hand, Sinclair sees that the goal can best be realized by examining events at levels intermediate between gene and behavior. This impresses me as a more promising approach. To realize its goals, behavior genetics needs to become neurogenetics. Selective breeding for extreme scores on a measure of interest to psychologists can help to understand the physiological bases of individual differences, as done in the work on avoidance learning by Brush (1991) and co-workers, for example.

Sinclair proposed a plausible and clever model of neural functions to explain a difference between two lines of rats selectively bred for response to a large injection of ethanol. By basing this model on established neurophysiological principles, he presents us with an hypothesis of considerable importance, especially if it

turns out to be true. I welcome his openess to suggestions for further refinements. This is refreshing in a field where explanatory models all too often are presented on a take-it-or-leave-it basis.

I would recommend several steps to strengthen the enterprise.

(1) Science at its best tests alternative hypotheses, not just a single null hypothesis. Genetic analysis has a profound weakness in its logic. Typically the results of a breeding experiment, for example, are predicted from a Mendelian model and then observations are tested against the model as null hypothesis. If the study is seeking a major gene effect, a test with low statistical power is more likely to affirm the null. Hence, a bad experiment is more likely to "discover" a gene. The remedy for this situation is to test several reasonable models and take one seriously only if the others can be rejected with confidence in light of the data. Alcohol has many effects throughout the body, and other hypotheses could and should be devised to explain the selection response.

(2) Once we have reasonable alternatives in mind, it should be possible to design effective experiments to test them. The author of an hypothesis has an obligation to tell us what it predicts and how it can be evaluated. If one selected line shows little response to ethanol, this might involve absorption, metabolism, and elimination of the drug as well as effects on neurons. The neural hypothesis might be examined *in vitro* using the hippocampal slice preparation.

(3) To have no evident behavioral effect of 2 mg/kg ethanol obviously requires some major adjustment of rat's physiology. It would be helpful to compare the selected lines to unselected controls, because it is possible that the high response line differs from controls for a different physiological reason than does the low line, especially if some of the relevant loci have dominance or if gene frequencies were very different at the outset of selection at different loci (which is quite possible unless a cross among inbred strains provided the foundation population). Furthermore, an inverse line difference as well as a positive line difference in a correlated response *could* be spurious and ought to be examined in crosses.

(4) A large response to selection typically involves several segregating loci. Because the place, time, and mechanism of action of a gene are highly specific, it is rather unlikely that there will be only one primary site of *gene* action relevant to a line difference.. Selective breeding is totally opportunistic and accumulates whatever differences are available to produce line divergence. These differences may be trivial from a psychological perspective or they may be illuminating. If the Syracuse High and Low Avoidance (SHA and SLA) lines, for example, showed a large difference in sensitivity to shock, this would be seen as a trivial result because an animal will not learn to avoid something which is not noxious. It turns out that the SHA versus SLA difference is much more interesting (Brush *et al.,* 1985; Brush, 1991), but this is essentially a matter of happenstance. On the other hand, selection for open-field activity under bright light yields lines which differ at the albinism locus (DeFries *et al.,* 1978), a result some regard as trivial. This could have been avoided by an auspicious choice of ancestral strains. These thoughts return us to point 1 about the need to test alternative possibilities. Generally speaking, I think the time for formal models comes after extensive tests have been done to characterize the differences between the selected lines on many dimensions.

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